Draw Pharmacology in your mind

If you are a pharmacy student
If you are postgraduate and want to revise pharmacology by an easy way
If you are using any pharmacology reference
this file will aid you
> And wait for more <

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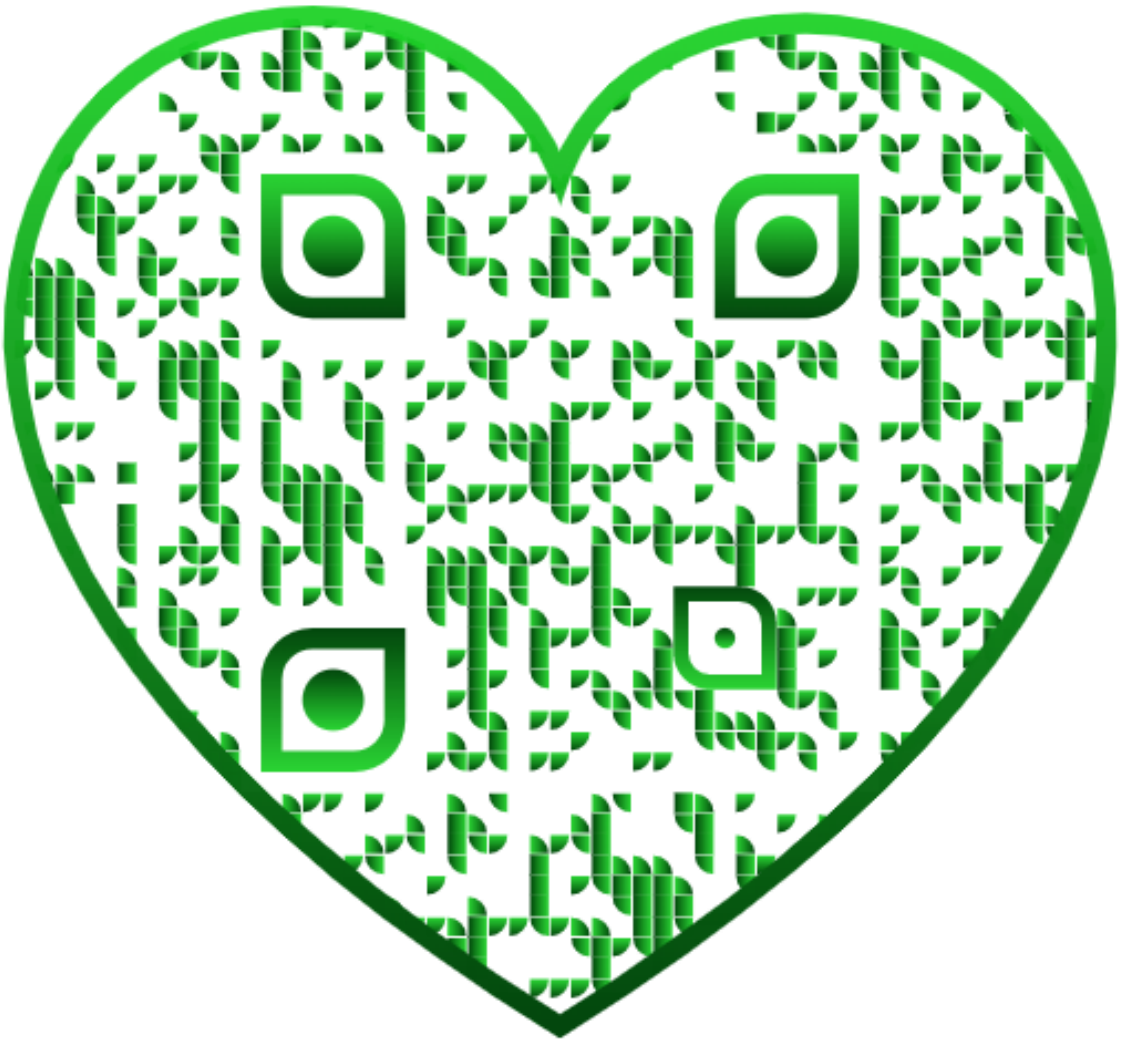
لا تنسونى من صالح دعائكم

Pharmacist. **Alaa Nasr** **د. آلاء نصر**



Parkinson's disease

Progressive neurodegenerative disease caused by **degeneration of dopaminergic neurons** in *substantia nigra*

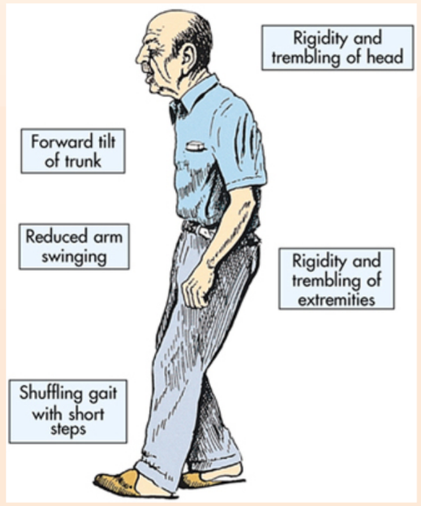
Symptoms

1. **Resting tremors** → affects all the limbs, neck, face and jaws
2. **Rigidity** → ⇑ tone and stiffness of the muscles → Mask-like face & Clog-like release of the muscles
3. **Bradykinesia** → slow movement → difficulty of initiating and maintaining movement
4. **Postural instability**
5. **Gait disorders** → shuffling small steps, sudden freezing
6. **Swallowing difficulty** (dysphagia)
7. **Speech disorders** (dysarthria)
8. **Small hand-writing** (micrographia)
9. Depression, Dementia, Sleep disturbances, Constipation

Catherine Metzger
13 October 1869

Etiology

1. Viral infection
2. Environmental cause (MPTP oxidative stress)
3. Genetic factor
4. Aging process
5. Drug induced Antipsychotics, Reserpine, Valproate, Metoclopramide (Primpran®)
6. CO - Injury - Atherosclerosis


Rigidity and trembling of head
Forward tilt of trunk
Reduced arm swinging
Rigidity and trembling of extremities
Shuffling gait with short steps

Causes

- In the **nigrostriatal pathway** → there is a **balance** between **DA** *(acting as an inhibitory neurotransmitter)* and **Ach** *(acting as an excitatory neurotransmitter)*
- The **basal ganglia** controls **motor activity** → so any *disturbance* in DA-Ach balance → would cause *movement disorders*
- As this disease is **neurodegenerative** → so it is **irreversible** → so any treatment is just used to treat the symptoms &/or slow down the degeneration → any treatment can not compensate the degeneration → so the treatment is **lifelong**
- The **symptoms** appear when the degeneration in the dopaminergic neurons occurs while cholinergic neurons are still intact (no degeneration)
- Average age of onset is **55 - 65 years**
- **Men** are more exposed to risk than women

Antiparkinsonians

1. Replacing dopamine

Levodopa

Levodopa is converted to dopamine *by* ***Dopa decarboxylase enzyme*** + ***Vit B_6*** *(in brain)* .. then **Dopamine will act on D_2** receptors in the nigrostriatal pathway to decrease parkinson's disease symptoms

Notice that

1. Dopa decarboxylase enzyme is found IN and OUT of the CNS .. that will lead to conversion of Levodopa before it reaches CNS !!
2. **Dopamine** can not be absorbed orally and can not pass Blood Brain Barrier (BBB) → so **not used as a drug**

Mechanism

1. Most of the dose is **metabolized by COMT in GIT** before its absorption
2. **Dopa decarboxylase converts Levodopa in the periphery** into dopamine *(before reaching CNS)* → and Dopamine *can not pass BBB*
3. Levodopa undergoes **large first-pass effect** *(metabolism)* → **95%** of the oral dose is metabolized in the liver before reaching the systemic circulation → so only **1-3%** of the administered dose will be available in the CNS

Disadvantages

Solution

Compining Levodopa with

1. Dopa decarboxylase inhibitor *(that **can not** pass BBB)*
2. COMT inhibitor

Dopa decarboxylase inhibitors

ex. Carbidopa - Benserazide

♦ They effectively ⇓ **the peripheral conversion of Levodopa into Dopamine** → *so ⇑ amount of Levodopa reaching CNS, ⇓ peripheral side effects, ⇓ dose of Levodopa*

♦ They **can not pass BBB** so do not affect the conversion in the brain

♦ Carbidopa ⇑ the amount of dopamine reaching CNS by **10%** → so ⇓ the dose of Levodopa by **75%**

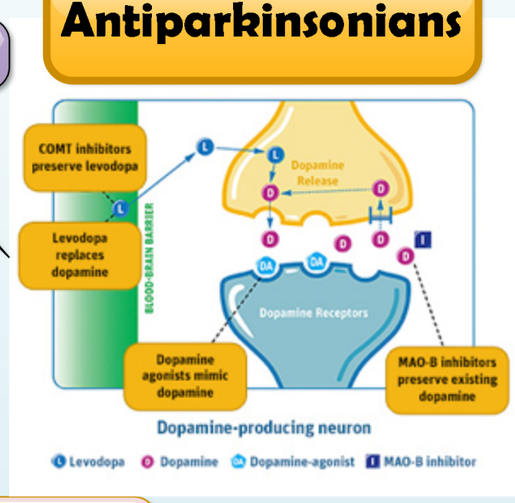
♦ ***Trade names*:**

Sinemet® = Levodopa + Carbidopa

Modapar® = Levodopa + Benserazide

Drug-Drug interactions

1. Vit B_6 (Pyridoxine) *(can catalyze more peripheral conversion)*
2. Antipsychotics *(opposite actions)*



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Pharmacological actions

The most effective drug used for parkinson's disease → decrease Parkinson's disease symptoms in the **nigrostriatal pathway**

But non-selective so will affect

1. Limbic system
2. Tuberohypophyseal system
3. Chemoreceptor trigger zone (CTZ)

so, causes many central side effects

Side effects

1. **On-Off effect (light switch)**
   - ♦ This usually occurs after **2 or more years of treatment**
   - ♦ **Cause** → fluctuation of level of Levodopa in the plasma due to its *very short half-life* (1-2 hours)
   - ♦ **Solution**
     1) Multiple small doses of Levodopa
     2) Administration of other antiparkinson's drug
     ex. *Talcapone - Selegiline - Bromocriptine*
2. **Dyskinesia** (Peak-dose dyskinesia)
   - ♦ Induction of involuntary movement as a result of high amount dopamine in the ***nigrostriatal pathway***
   - ♦ **Cause** → High dose of Levodopa
3. **Nausea and vomiting** due to **CTZ** stimulation
4. **Endocrine effect** inhibition of **Prolactin** hormone secretion
5. **Psychological effect** due to action on **limbic system**

Antiparkinsonians

2. Mimic dopamine

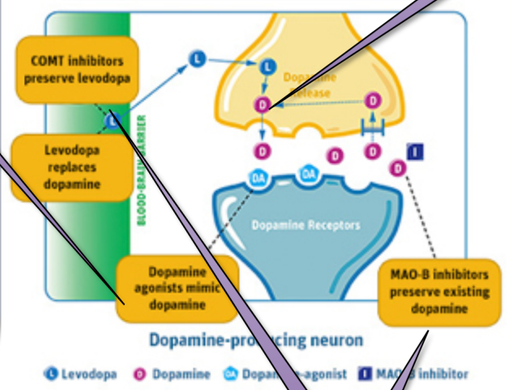
Examples

Bromocriptine - Pergolide → activate D_2 receptors
Pramipexole - Rapinirol → activate D_2 & D_3 receptors

Uses

Can be used in:
1. **Early stages** of Parkinson's disease → to *compensate loss of Dopamine* and *delay the need to Levodopa*
2. **Late stages** of Parkinson's disease → as there are *small amount of dopaminergic neuron* → so Levodopa will not be effective in this case

Note that .. Pramipexole can be combined with **Levodopa** to decrease **on-off effect**



4. Releasing more Dopamine

Examples

Amantadine (antiviral drug treating influenza)

Mechanism

1. ⇑ **the release** of Dopamine (from its stores) in the nigrostriatal neurons
2. ⇓ **neuronal reuptake** of Dopamine in nigrostriatal pathway

Uses

1. **Early** and **mild** cases of Parkinson's disease
2. In **combination** with **Levodopa**

3. ⇓ Metabolism of Dopamine

MAO-B inhibitors

Examples

Rasagiline → once daily
Selegiline → Twice daily

Mechanism

They selectively inhibit MAO-B enzyme leading to:
1. ⇑ **Dopamine** level in basal ganglia
2. ⇓ **the formation of H_2O_2** *(produced from Dopamine metabolism by MAO-B)* → so ⇓ the free radicals formed from H_2O_2 which cause degeneration of neurons in Parkinson's disease
3. ⇓ **progression** of Parkinson's disease that results from environmental toxins such as MPTP by preventing its conversion to toxic metabolite

Uses

1. **Early** and **mild** cases of Parkinson's disease
2. In **combination** with **Levodopa** to
   - ⇓ dose and side effects of Levodopa
   - ⇓ **on-off effect**
3. **Neuroprotective** drugs decreasing progression of Parkinson's disease *(⇓free radicals and MPP^+)*

COMT inhibitors

Examples

Talcapone - Entacapone

Mechanism

- **Inhibit COMT enzyme** which is responsible for → metabolism of Levodopa in the **GIT and liver** into O-methyl dopa
- So, these drugs ⇑ **the oral bioavailability and half-life** of oral dose of levodopa by **2 folds** → ⇑ *effectiveness of treatment by Levodopa*

Uses

Talcapone is reserved for patients suffering from **on-off** effect or **poorly controlled by Levodopa**

5. ⇓ Acetylcholine action

Examples

Benzatropine (Cogintol®)
Trihexphenidyl (Parkinol®)
Biperiden (Akineton®)

Mechanism

1. **Blocking action of Ach** in corpus striatum
2. ⇓ neuronal reuptake of Dopamine

Notice that .. they are more effective in decreasing **tremors** than any other symptoms in Parkinson's disease

Uses

1. **In combination with Levodopa**
2. **Instead of Levodopa in case of:**
   1) Levodopa is **not tolerated** due to its side effects
   2) In **late stages** of Parkinson's disease
   3) For Parkinson's patient **receiving antipsychotic** (Dopamine antagonist) that cancels the effect of Levodopa !

Adverse effects

1. Dry mouth
2. Blurred vision
3. Constipation
4. Urine retention
5. Glaucoma

(Atropine-like action)

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Useful figures

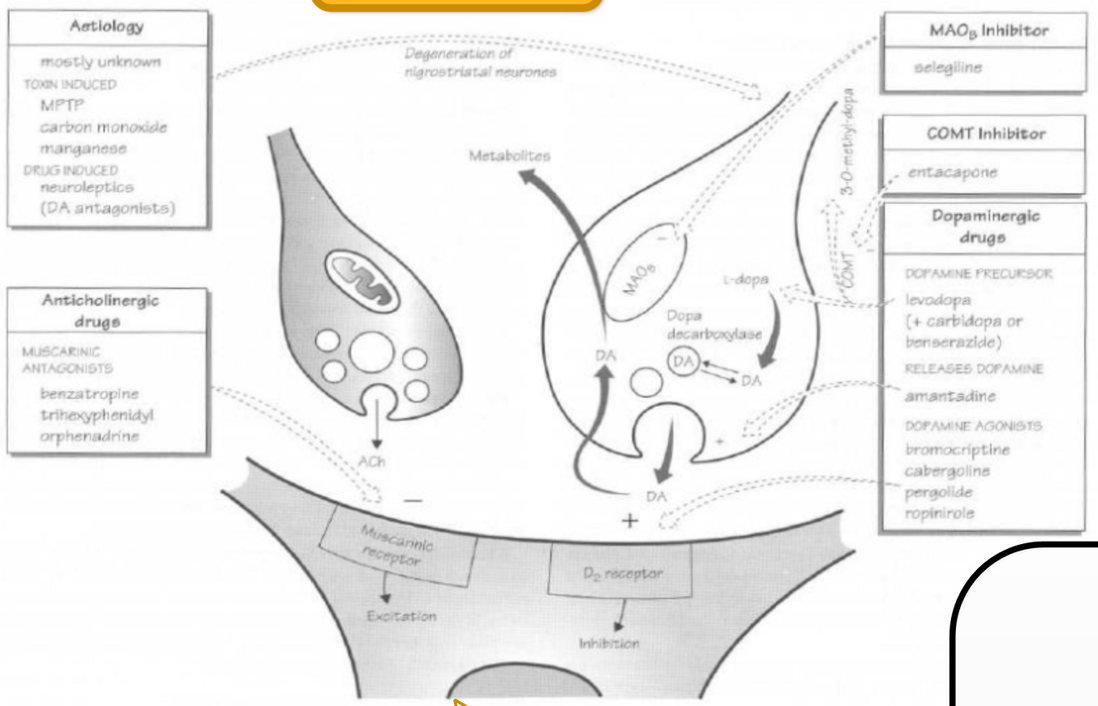
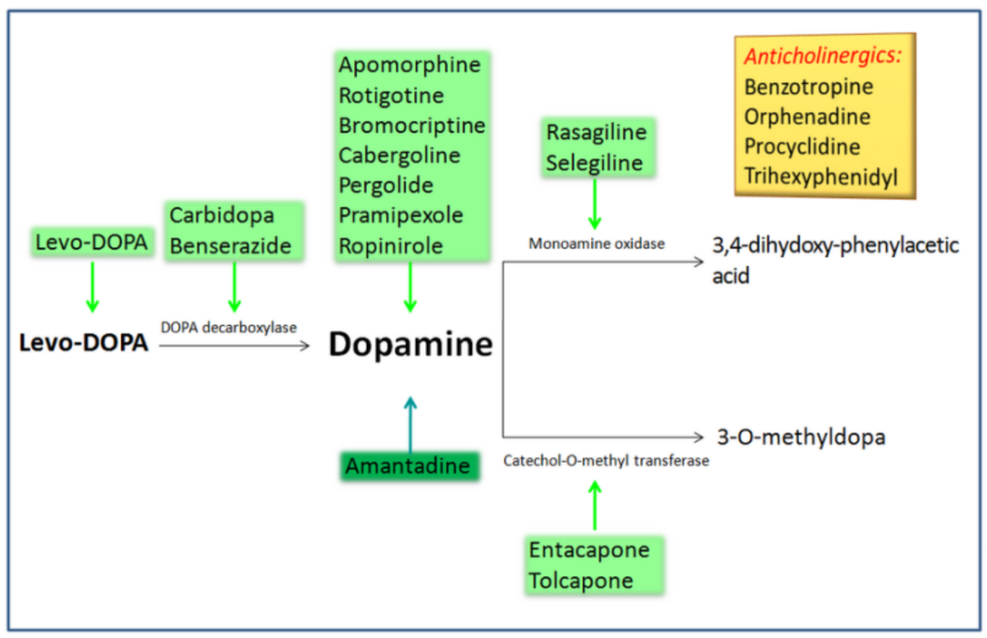
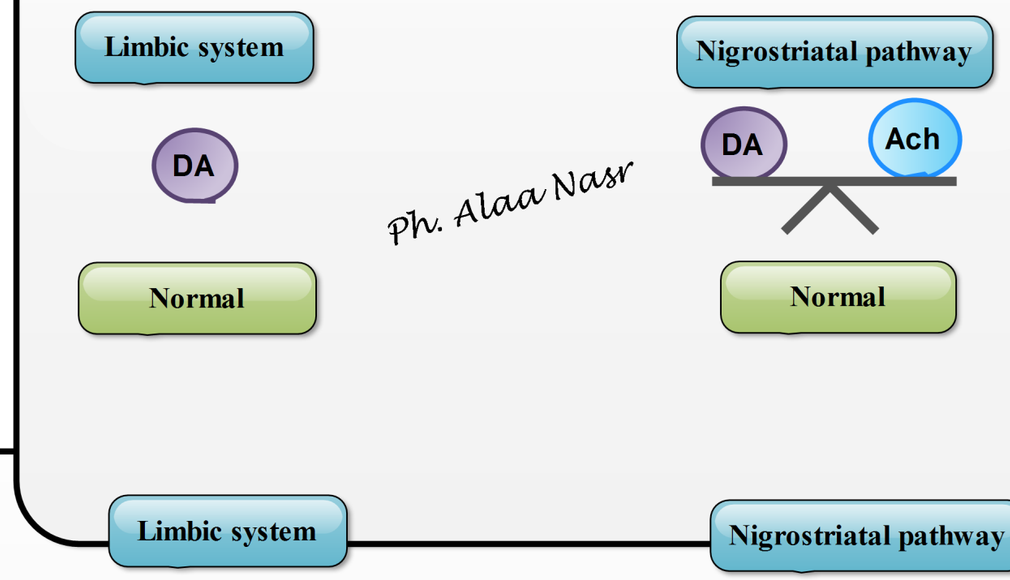
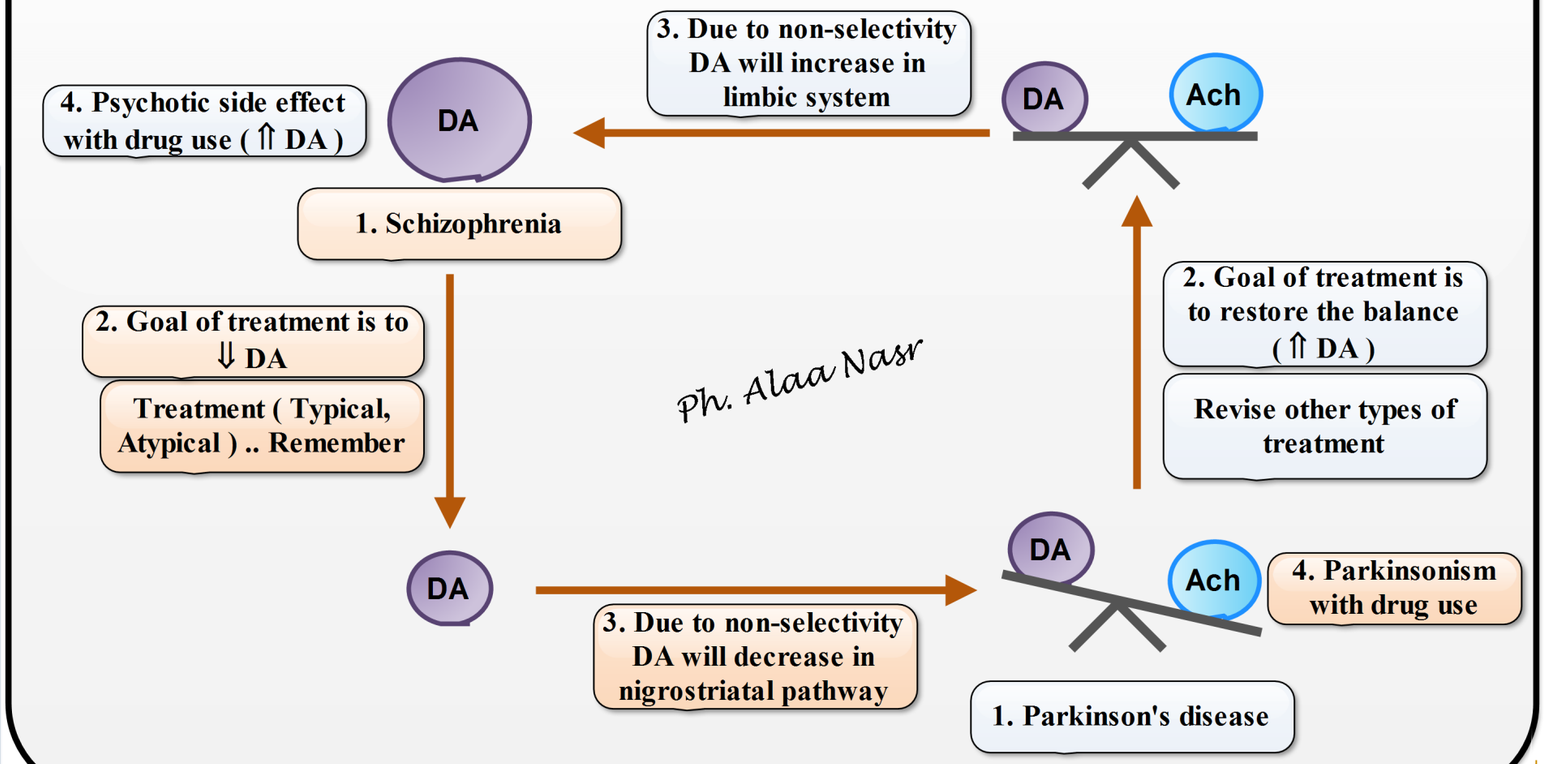


Figure illustrating mechanisms of drugs treating Parkinson's disease from "Medical pharmacology at a glance"



Relation between Parkinson's disease and Schizophrenia (Simplified)




3. Due to non-selectivity DA will increase in limbic system
4. Psychotic side effect with drug use (⇑ DA)
DA
DA
Ach
1. Schizophrenia
2. Goal of treatment is to ⇓ DA
Treatment (Typical, Atypical) .. Remember
Ph. Alaa Nasr
2. Goal of treatment is to restore the balance (⇑ DA)
Revise other types of treatment
DA
DA
Ach
4. Parkinsonism with drug use
3. Due to non-selectivity DA will decrease in nigrostriatal pathway
1. Parkinson's disease